REMARKS

Claims 1-4, 7-11, 13, 14, 16, 17, and 50-72 are pending and currently under examination.

Claim 57 has been amended to recite "*in vivo*". This amendment adds no new matter and is supported throughout the application as filed.

The Office Action Summary of the December 7, 2006 Office action has box "2a" check, which indicates that the Office Action is final. Applicants thank the Examiner for clarifying that the Office Action is non-final in the phone discussion on December 13, 2006.

The rejections are addressed in the order presented in the December 7, 2006 Office Action.

Rejection of claims 1-4, 7-11, 13, 14, 16, 17, 22-26, 29-32, 50-56, and 70-72

The rejection of claims 1-4, 7-11, 13, 14, 16, 17, 22-26, 29-32, 50-56, and 70-72 as allegedly obvious is maintained. Applicants have traversed this rejection for reasons of record. In brief, as previously explained, the law is clear: knowledge of general methods, in this case sequencing of V_H and V_L regions of antibodies, does not render any particular sequence obvious. The designation "RFB4" by Shen *et al.*, which was cited by the Patent Office as teaching an RFB4-producing hybridoma, provides no structural information regarding the sequence of the antibody. Even if one of skill assumes that the hybridoma of Shen *et al.* is the same as the hybridoma used in the current application, the combination of cited references does not predict the RFB4 V_H and V_L sequences of SEQ ID NO:2 and SEQ ID NO:4, respectively. Last, even assuming *arguendo* that the claims could be considered *prima facie* obvious, the claims are patentable due to surprising and superior properties of the claimed RFB4-ds(Fv) immunoconjugates.

In the FitzGerald Declaration filed March 11, 2004, Dr. FitzGerald compares the RFB4 immunotoxin to the closest prior art, an immunotoxin made with another antibody to CD22, LL2. Although chemical conjugates comprising LL2 or LL2(Fab') joined to truncated PE were very cytotoxic toward Burkitt's lymphoma cell lines in cell culture and exhibited significant

anti-tumor activity in nude mice bearing solid subcutaneous Burkitt's lymphoma tumors, attempts to make single chain scFV and dsFv failed. Dr. FitzGerald explains that one of skill could not predict which particular immunoconjugates would exhibit superior expression characteristics and stability.

The Examiner acknowledges the declaration, but believes that it is not persuasive, citing Reiter *et al.* (*Nature Biotechnology*) on p. 1243 as showing that 4 out of 8 dsFv immunotoxins had improved binding affinity. Applicants disagree with this interpretation of the cited passage, however. The improved binding affinity in the passage referred to by the Examiner is relative to scFv, not relative to the starting IgG. Dr. FtizGerald attests to the fact that the finding that RFB4 immunotoxins retain the binding specificity and affinity of the parent RFB4 IgG is unusual. Applicants submit that the binding of the dsFv immunoconjugates is equivalent to the parent IgG in only a minority of the cases. No rationale for predicting which immunoconjugates would exhibit this property is provided, either in the cited art or by the Examiner. Thus, the superior binding properties and cytotoxicity of the claimed anti-CD22 immunoconjugates are unexpected and surprising.

In addition, Dr. FitzGerald explains that the superior toxicity and efficacy of RFB4ds(Fv)-PE38 that was observed not only in animal models, but also in human Phase I trials (referring to his previous Rule 1.132 Declaration, signed May 15, 2001, which is of record in this application) was surprising and could not be predicted from the art (sections 9 and 10) of the March 11, 2004 FitzGerald Declaration. Indeed, the clinical trials referred to by Dr. FitzGerald showed that eleven patients achieved complete remission and two patients achieved partial remission when RFB4ds(Fv)-PE28 was administered to them (section 10 of the FitzGerald Declaration signed May 15, 2001). The Examiner provides no evidence or reasoning as to why one of skill would predict such superior properties.

A *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties (*In re Papeschi*, 315 F.2d281, 137 USPA43 (CCPA 1953)). Further, evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness (MPEP § 2144.08.II.B,

citing *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987)). Here, the facts are analogous to those of *In re Chupp*. In the fact pattern explained in *In re Chupp*, Chupp submitted declarations discussing the results of tests comparing the herbicidal activity of the compounds at issue with the closet prior art compounds on the ability to control two weeds in two crops. The declarations included statements noting the superior performance of the claimed compositions. In rejecting the claims, the examiner said that more extensive comparative testing was needed because the data disclosed in the specification showed that the claimed compound would not be superior to prior art compounds for crops other than corn or soybeans. The board affirmed the rejection. In arguing before the Federal Circuit, the Solicitor took the position that a compound is patentable only if its subject matter as a whole would not have been obvious, and dismissed the claimed compounds' superiority with respect to corn and soybeans, noting that its herbicidal utility in other crops was only mediocre, which according to the Solicitor, represented its properties "as a whole". The Federal Circuit disagreed. The Court held that "[t]o be patentable, a compound need not excel over prior art compounds in all common properties....Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness." This is precisely the situation here. Even though RFB4-dsFv may share common properties with other dsFV compounds that are developed to target molecules on cancer cells, such as CD22, the remarkable results in terms of retention of an affinity that is essentially the same of the parent IgG and the clinical efficacy observed using the RFB4-dsFV constructs in patients is sufficient to render the claims patentable.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Rejection of claims 57-69

Claims 57-69 are newly rejected as allegedly obvious over Ghetie *et al.* in view of Shen *et al.*, Reiter *et al.* (*Biochemistry*), and Kuan *et al.* The Examiner contends that Ghetie *et al.* teach RFB4-ricin A chemical conjugates that inhibit growth of B-cell lymphomas in mice. Shen *et al.* is described in the Office Action as teaching a hybridoma that produces an antibody

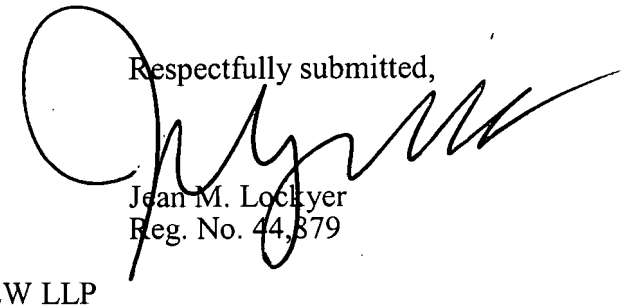
called RFB4, and further, as suggesting that RFB4 could be used for therapeutic purposes because of its potency. Reiter *et al.* and Kuan *et al.* are each cited as teaching dsFv constructs linked to PE. The Examiner alleges that it would have been obvious based on the cited references to have arrived at the claimed methods for inhibiting the growth of malignant B-cells that express a CD22 molecule on the surface of the cell. Applicants respectfully traverse this rejection.

Claims 57-69 are patentable for the same reasons that the compositions claims are patentable. Furthermore, as Applicants have previously explained, the conjugates exhibit surprising efficacy when used *in vivo*. Dr. FitzGerald presented clinical data showing that leukemia patients with $CD22^+$ leukemia cells who were administered BL22 (an RFB4dsFV-PE conjugate) went into remission. Most of them had a complete remission. Indeed, these data were remarkable enough to warrant publication in the *New England Journal of Medicine* (*N. Engl. J. Med.* 345:241247, 2001, copy attached). The Office Action provides no reasoning or evidence that the claimed methods would have been expected by one in the art to provide this exceptional level of efficacy in treating $CD22^+$ B cell malignancies. Accordingly, claims 57-69 are additionally patentable. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe all claims now pending in this Application are in condition for allowance. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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